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Comparative Efficacy of Tirzepatide Versus GLP-1 Receptor Agonists on Glycaemic Control and Body Weight in Adults With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Head-to-Head Randomised Controlled Trials

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Systematic Review

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Abstract

Purpose

Dual incretin receptor agonists targeting GIP and GLP-1 receptors represent a novel therapeutic approach for the management of type 2 diabetes mellitus. Tirzepatide, the first agent in this class, has demonstrated substantial metabolic benefits compared with selective GLP-1 receptor agonists. This study aimed to compare the efficacy of tirzepatide versus single GLP-1 receptor agonists on HbA1c and body weight in adults with T2DM.

Methods

A systematic review and meta-analysis was conducted in accordance with PRISMA guidelines to compare tirzepatide with GLP-1 RAs in adults with T2DM. Randomised controlled trials with a minimum duration of 24 weeks were included. Outcomes were changes in HbA1c (%)and body weight (kg). Random-effects meta-analyses were performed with dose-stratified subgroup analyses for tirzepatide 5 mg, 10 mg, and 15 mg.

Results

Five randomised controlled trials were included. Compared with GLP-1 RAs, tirzepatide achieved greater reductions in HbA1c across all doses, with pooled mean differences ranging from − 0.89% to − 0.95%. Individual trials demonstrated greater HbA1c reductions with increasing tirzepatide dose. Body-weight reduction showed a clear dose-sensitive response, with pooled mean differences of − 6.2 kg at 5 mg, − 8.6 kg at 10 mg, and − 10.7 kg at 15 mg versus GLP-1 RAs.

Conclusion

In adults with T2DM, tirzepatide provides superior glycaemic and weight-loss efficacy compared with GLP-1 receptor agonists. While both outcomes demonstrate dose-responsive effects, body-weight reduction shows greater sensitivity to dose escalation, supporting dose-tailored treatment strategies.

1. Introduction

1.1. Background

Type 2 diabetes mellitus (T2DM) is a major and growing global health problem. Around 589 million adults aged 20–79 years are currently living with diabetes worldwide, accounting for roughly 11% of the global adult population [1]. The burden is projected to increase substantially over the coming decades, with the number of adults affected expected to reach approximately 853 million by 2050[1]. As T2DM

constitutes the vast majority of diabetes cases, it is a leading contributor to premature morbidity and mortality through its association with microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular disease (ischaemic heart disease, stroke, peripheral arterial disease) [2]. This escalating prevalence places a substantial strain on individuals, healthcare systems, and economies.

1.2. Pathophysiology and Current Management of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus develops through the combined effects of insulin resistance and a progressive decline in pancreatic beta cell function. In the early stages, peripheral tissues such as skeletal muscle, liver and adipose tissue become less responsive to insulin, leading to a compensatory rise in insulin secretion. Over time this compensation fails as chronic metabolic stress impairs beta cell performance and reduces insulin output [2]. Excess body weight, particularly central adiposity, is a major contributor to this process. Visceral fat releases increased free fatty acids and pro-inflammatory mediators that interfere with insulin signalling and promote systemic insulin resistance [2]. In parallel, chronic nutrient excess, oxidative stress and endoplasmic reticulum stress accelerate beta cell dysfunction and trigger pathways that lead to cell exhaustion and apoptosis [3]. Hepatic insulin resistance results in inappropriate gluconeogenesis, while impaired insulin action in adipose tissue allows continued lipolysis, raising circulating fatty acids and placing further strain on beta cells [3]. Additional disturbances such as a reduced incretin effect, hyperglucagonemia, altered gut microbiota and increased renal glucose reabsorption further disrupt glucose homeostasis, producing the persistent hyperglycaemia characteristic of type 2 diabetes [2].

Management of type 2 diabetes mellitus (T2DM) begins with lifestyle modification, including dietary changes, increased physical activity and weight optimisation, which form the foundation of long-term care [4]. When lifestyle measures are insufficient, metformin is recommended as first-line therapy because of its efficacy, safety profile and weight-neutral effect [4]. If glycaemic targets are not met, additional agents are selected based on individual clinical needs. Commonly used options include dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium–glucose cotransporter-2 inhibitors (SGLT2i), sulfonylureas and insulin, with SGLT2i preferred in patients with high cardiovascular or renal risk due to their protective benefits [4]. Although these therapies can improve glycaemia, treatment limitations such as hypoglycaemia risk, weight gain, modest durability of response or inadequate HbA1c reduction are frequently encountered in practice [5]. As a result, recent therapeutic development has focused on agents that not only lower glucose effectively but also support clinically meaningful weight reduction.

1.3. Incretin-Based Therapies in Type 2 Diabetes

Incretin-based therapies have emerged as an important advance in this direction. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) enhance glucose-dependent insulin secretion while promoting appetite regulation and weight loss, and newer formulations have demonstrated superior metabolic effects [6]. Building on this progress, dual incretin agonists that target both glucose-dependent insulinotropic

polypeptide (GIP) and GLP-1 receptors represent a further step toward more comprehensive metabolic management [6].

1.4. Tirzepatide as a Dual Incretin Receptor Agonist

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as liraglutide, dulaglutide and semaglutide act by stimulating the GLP-1 receptor, a class B G-protein-coupled receptor expressed in pancreatic islets, the gastrointestinal tract and central appetite-regulating regions [7, 8]. Activation of this receptor enhances glucose-dependent insulin secretion and supports β-cell function, while simultaneously suppressing glucagon release from α-cells, reducing hepatic glucose output and improving fasting and post-prandial glycaemia [7]. In addition, GLP-1 RAs delay gastric emptying, thereby attenuating post-prandial glucose excursions, and act on hypothalamic pathways to promote satiety and reduce caloric intake, contributing to weight loss [7, 8]. Long-acting analogues such as dulaglutide and semaglutide incorporate structural modifications that extend their half-life by resisting dipeptidyl peptidase-4 degradation and enhancing protein binding, allowing sustained receptor activation with once-weekly dosing [7, 8]. These integrated actions on insulin secretion, glucagon suppression, gastric motility and appetite regulation underpin the clinically meaningful reductions in glycated haemoglobin (HbA1c) and body weight achieved with GLP-1 RAs [7].

Tirzepatide is a dual incretin receptor agonist engineered to activate both the glucose-dependent insulinotropic polypeptide (GIP) receptor and the GLP-1 receptor, thereby engaging complementary hormonal pathways central to glucose and energy regulation [9]. Its GLP-1 receptor activation reproduces the core effects of GLP-1 RAs, including enhanced glucose-dependent insulin secretion, reduced glucagon secretion, slowed gastric emptying and appetite suppression [9–11]. Pharmacological GIP receptor stimulation adds metabolic actions not achieved by GLP-1 activation alone. GIP enhances insulin sensitivity in adipose tissue, improves post-prandial lipid handling and contributes to energy regulation, amplifying weight-loss effects when combined with GLP-1 signalling [9–11]. Although endogenous GIP responsiveness is diminished in type 2 diabetes, sustained pharmacological stimulation can restore the insulinotropic effect of GIP and further improve post-prandial glycaemia [10, 11]. Evidence from comparative studies shows that the combined activation of GIP and GLP-1 receptors produces additive and synergistic effects on glycaemic control, body weight and metabolic function, leading to greater reductions in HbA1c and body weight than those achieved with selective GLP-1 RAs alone [11]. Through this dual-pathway mechanism, tirzepatide addresses multiple metabolic defects of type 2 diabetes more effectively than single-incretin therapies.

1.5. Rationale for this Review

Previous systematic reviews evaluating tirzepatide have differed in scope and methodological focus. Some reviews focused primarily on weight-loss outcomes [11, 12] while two reviews assessed both HbA1c and body weight using broader analytical frameworks [13, 14] that included mixed comparator groups and indirect comparisons. These reviews also incorporated studies with short follow-up durations of as little as eight weeks and relied on a limited number of head-to-head trials, with some

dose groups represented by only one or two studies. As multiple head-to-head randomised controlled trials directly comparing tirzepatide with individual GLP-1 receptor agonists in adults with type 2 diabetes are now available, a focused synthesis based on direct comparisons allows clearer assessment of glycaemic and weight effects.

1.6. Objectives

To compare the efficacy the newly approved incretin therapy tirzepatide with a single GLP-1 agonist in adults with type 2 diabetes mellitus (T2DM), by pooling clinical trial evidence measuring change in HbA1c and change in body weight.

2. Methods

2.1. Study Design and PICO

This study was conducted as a systematic review and meta-analysis to evaluate the comparative efficacy of dual incretin receptor agonists versus single glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in adults with type 2 diabetes mellitus (T2DM). The review was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. The review protocol was not prospectively registered in PROSPERO; however, the eligibility criteria, outcomes, and analytical approach were defined prior to data extraction to minimise the risk of selective reporting.

The research question was structured using the PICO framework:

- Population: Adults (≥ 18 years) with type 2 diabetes mellitus
- Intervention: Dual incretin receptor agonists (dual GIP/GLP-1 receptor agonists (tirzepatide)
- Comparator: Single GLP-1 receptor agonists
- Outcomes: Reduction in glycated haemoglobin (HbA1c, %) and reduction in body weight (kg)
- Study design: Randomised controlled trials with a minimum duration of 24 weeks

2.2. Search Strategy

A comprehensive literature search was conducted in PubMed (MEDLINE), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception to 31 October 2025. Searches were restricted to human studies, English-language publications, and randomised controlled trials.

Search strategies combined controlled vocabulary terms and free-text keywords related to GLP-1 receptor agonists, dual incretin receptor agonists, and type 2 diabetes mellitus.

The detailed search strings used for each database were as follows.

For PubMed (MEDLINE), filters applied were English language, human studies, and randomised controlled trials. The search strategy was: ("Glucagon-Like Peptide 1 Receptor Agonists"[Mesh] OR "GLP-1 receptor agonist" OR "incretin mimetic" OR semaglutide OR liraglutide OR dulaglutide OR exenatide OR lixisenatide OR albiglutide) AND ("GIP receptor agonist" OR "dual agonist" OR "dual incretin" OR "GIP/GLP-1" OR tirzepatide OR mazdutide OR retatrutide) AND ("Type 2 Diabetes Mellitus"[Mesh] OR "type 2 diabetes" OR T2DM) AND (compar* OR versus OR vs OR "head to head"). This search retrieved 51 records.

For Embase, filters applied were English language, human studies, and randomised controlled trials. The search strategy was: ('glucagon like peptide 1 receptor agonist'/exp OR 'glp 1 receptor agonist':ab,ti OR 'glp-1 analogue':ab,ti OR 'incretin mimetic':ab,ti OR semaglutide:ab,ti OR liraglutide:ab,ti OR dulaglutide:ab,ti OR exenatide:ab,ti OR lixisenatide:ab,ti OR albiglutide:ab,ti) AND ('dual agonist':ab,ti OR 'dual incretin':ab,ti OR 'gip receptor agonist':ab,ti OR 'gip/glp-1':ab,ti OR tirzepatide:ab,ti OR mazdutide:ab,ti OR survodutide:ab,ti OR retatrutide:ab,ti OR sar425899:ab,ti) AND ('type 2 diabetes mellitus'/exp OR 'type 2 diabetes':ab,ti OR t2dm:ab,ti) AND (compar*:ab,ti OR versus:ab,ti OR 'head to head':ab,ti OR vs:ab,ti). This search retrieved 61 records.

For the Cochrane Central Register of Controlled Trials (CENTRAL), the search strategy was: (Tirzepatide OR Mounjaro OR Zepbound OR SAR425899 OR LY3298176) AND (liraglutide OR semaglutide OR dulaglutide OR exenatide OR albiglutide OR efpeglenatide OR "GLP-1 receptor agonist*" OR "GLP 1" OR "glucagon-like peptide-1") AND (incretin* OR GIP OR "gastric inhibitory polypeptide" OR "glucose-dependent insulinotropic peptide" OR "dual agonist" OR "dual incretin" OR coagonist* OR "GIP/GLP-1") AND (HbA1c OR "glycated hemoglobin" OR "A1C" OR "glycemic control" OR weight OR "weight loss" OR "body mass index" OR BMI OR obes* OR "body weight") in title, abstract, and keyword fields. Word variations were included. This search retrieved 202 records.

2.3. Eligibility Criteria

Randomised controlled trials were eligible if they included adults with type 2 diabetes mellitus and compared a dual incretin receptor agonist with a single GLP-1 receptor agonist. Studies were required to have a minimum treatment duration of 24 weeks and to report reduction in HbA1c and or reduction in body weight as outcomes.

Studies were excluded if they were non-randomised, observational, post hoc analyses, conducted in non-diabetic populations or lacked an active GLP-1 receptor agonist comparator. No restrictions were applied based on sex, ethnicity, baseline body mass index, or background glucose-lowering therapy.

2.4. Study Selection Process

All records were identified through searches of the specified databases. Within each database, records were initially assessed based on titles and available abstracts to exclude clearly irrelevant studies. The remaining records were then combined, and duplicate entries were removed. The records subsequently underwent further screening, followed by full-text assessment against the predefined inclusion and

exclusion criteria. Studies meeting all eligibility criteria were included in the final systematic review and meta-analysis. The study selection process is summarised in the PRISMA flow diagram.

2.5. Data Extraction

Data were extracted using a predefined and standardised data extraction form independently by both authors. Study-level characteristics and outcome-level data were summarised in two structured tables. Extracted datas were cross-checked for accuracy and completeness. Where discrepancies were identified, the original trial reports and supplementary materials were reviewed, and final values were agreed upon through discussion.

Extracted study characteristics included trial registration number, study setting, duration of follow-up, intervention and comparator details, sample size per study arm, and funding source. Extracted efficacy outcomes included reduction in glycated haemoglobin (HbA1c, %) and reduction in body weight (kg) from baseline to study endpoint. Exact numerical values used for meta-analysis were obtained from trial publications and verified against clinical trial registry records where available.

2.6. Risk of Bias Assessment

The methodological quality of included studies was assessed using the Cochrane Risk of Bias tool for randomised controlled trials (RoB 2.0). Each study was evaluated across all prespecified domains, and overall risk-of-bias judgements were used to inform interpretation of the findings [16].

2.7. Data Analysis

Meta-analyses were performed using Review Manager (RevMan), version 5.4.1. Continuous outcomes, including reduction in HbA1c (%) and reduction in body weight (kg), were pooled using mean differences with corresponding 95% confidence intervals.

Analyses were conducted using a dose-stratified subgroup approach, with tirzepatide treatment arms grouped by dose (5 mg, 10 mg, and 15 mg) and analysed as separate subgroups. This approach ensured that comparator groups were not repeated within pooled estimates. A random-effects model was used to account for anticipated clinical and methodological heterogeneity.

Statistical heterogeneity was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. A two-sided p value of < 0.05 was considered statistically significant. Differences between dose subgroups were assessed using the χ^2 test for subgroup differences.

3. Results

3.1. Study Selection

The electronic database searches were conducted from database inception to 31 October 2025 and identified a total of 314 records, including 202 records from the Cochrane Central Register of Controlled

Trials, 61 from Embase, and 51 from PubMed. During the initial identification stage, records were assessed based on titles and available information within each database to exclude clearly irrelevant studies, resulting in 51 records being retained for further screening. The remaining records were then combined, and duplicate entries were removed. Following deduplication, records were screened by matching the study population, intervention, and comparator against the predefined eligibility criteria, with records not meeting these criteria excluded at this stage. This screening process resulted in 13 reports being identified as potentially eligible and sought for retrieval. Full-text assessment was subsequently performed against the predefined inclusion and exclusion criteria, leading to the exclusion of eight studies, including two due to insufficient study duration (< 24 weeks) and six due to incomplete or ongoing trial status. Ultimately, five randomised controlled trials met all eligibility criteria and were included in the final systematic review and meta-analysis. The study selection process is summarised in the PRISMA flow diagram (Fig. 1).

3.2. Study Characteristics

Five randomised controlled trials were included in the systematic review and meta-analysis. All trials evaluated tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, in comparison with a single GLP-1 receptor agonist in adults with type 2 diabetes mellitus.

Comparator agents included dulaglutide and semaglutide, administered at approved once-weekly doses. Among the included studies, three trials evaluated tirzepatide across multiple dose levels (5 mg, 10 mg, and 15 mg) [17–19], whereas two trials evaluated a single fixed dose of tirzepatide [20, 21]. This allowed both overall and dose-stratified analyses to be performed.

Study durations ranged from 26 to 52 weeks. Trials were conducted in multicentre international settings, as well as in Japan and Germany. Sample sizes varied across studies, reflecting differences in trial design and scope. All included trials were sponsored by Eli Lilly and Company. Detailed trial characteristics are summarised in Table 1.

Baseline characteristics and outcome data extracted for quantitative synthesis, including baseline values and mean reductions in glycated haemoglobin (HbA1c) and mean reductions in body weight, are presented in Table 2.

3.3. Risk of Bias Assessment

Risk of bias was assessed for all included studies using the Cochrane Risk of Bias 2.0 tool. Judgements were made across the five prespecified domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. A summary of domain-level and overall risk of bias assessments is presented in Fig. 2.

Across the included trials, bias arising from the randomisation process was judged to be low risk in all studies [17–21]. Bias in measurement of the outcome and bias in selection of the reported result were also consistently assessed as low risk across all trials [17–21].

Bias due to deviations from intended interventions was judged to be low risk in most studies; however, one trial was assessed as being at high risk in this domain [20]. Bias due to missing outcome data showed greater variability, with two studies judged to be at low risk [17, 18], one study assessed as having some concerns [21], and two studies judged to be at high risk [17, 18].

Overall risk of bias was judged to be low in two studies [17, 18], high in two studies [19, 20], and to raise some concerns in one study [21]. The distribution of risk-of-bias judgements across domains and the overall assessments are illustrated in Fig. 2.

3.4. Effects on Glycaemic Control (HbA1c Reduction)

Across all included randomised controlled trials, tirzepatide at all analysed doses produced greater reductions in HbA1c compared with single GLP-1 receptor agonists. When examined at the individual study level, absolute HbA1c reductions with tirzepatide increased numerically with higher doses within the same trial. In comparisons with dulaglutide, larger HbA1c reductions were observed at 10 mg and 15 mg compared with 5 mg, and a similar numerical pattern was seen in trials comparing tirzepatide with semaglutide. The magnitude of HbA1c reduction varied across studies and comparator regimens, reflecting differences in comparator dose intensity (Table 2).

Meta-analysis was performed to evaluate the effect of tirzepatide on reduction in glycated haemoglobin (HbA1c) compared with single GLP-1 receptor agonists. Five randomised controlled trials were included in the quantitative synthesis [17–21]. Analyses were conducted using a random-effects model and stratified by tirzepatide dose (5 mg, 10 mg, and 15 mg) to avoid duplication of comparator arms.

Five studies [17–21] contributed data to the 15 mg subgroup, including a total of 813 participants in the tirzepatide group and 813 participants in the comparator group. Tirzepatide 15 mg resulted in a significantly greater reduction in HbA1c compared with single GLP-1 receptor agonists, with a pooled mean difference of − 0.94% (95% CI − 1.36 to − 0.51). The overall effect was statistically significant ($Z = 4.33$, $p < 0.0001$), with substantial heterogeneity observed ($I^2 = 95\%$).

Three studies [17–19] contributed data to the 10 mg subgroup, comprising 658 participants receiving tirzepatide and 667 participants receiving comparator therapy. Tirzepatide 10 mg was associated with a significantly greater reduction in HbA1c compared with single GLP-1 receptor agonists, with a pooled mean difference of − 0.89% (95% CI − 1.45 to − 0.33). The overall effect was statistically significant ($Z = 3.11$, $p = 0.002$), and substantial heterogeneity was present ($I^2 = 95\%$).

Three studies [17–19] contributed data to the 5 mg subgroup, including 666 participants in the tirzepatide group and 667 participants in the comparator group. Tirzepatide 5 mg demonstrated a significantly greater reduction in HbA1c compared with single GLP-1 receptor agonists, with a pooled

mean difference of − 0.95% (95% CI − 1.17 to − 0.74). The overall effect was statistically significant (Z = 8.56, p < 0.00001), with moderate heterogeneity observed (I^2 = 69%).

No significant differences were observed between dose subgroups (χ^2 = 0.05, df = 2, p = 0.98; I^2 = 0%). The forest plot summarising the pooled estimates for HbA1c reduction across dose subgroups is presented in Fig. 3A.

3.5. Effects on Body-Weight Reduction

Across all included randomised controlled trials, tirzepatide at all analysed doses produced greater reductions in body weight compared with single GLP-1 receptor agonists. At the individual study level, absolute weight loss with tirzepatide increased numerically with higher doses within the same trial. In comparisons with dulaglutide, greater weight reductions were observed at 10 mg and 15 mg compared with 5 mg, and a similar numerical pattern was reported in trials comparing tirzepatide with semaglutide. The magnitude of weight reduction varied across studies and comparator regimens, with differences in comparator dose intensity observed across trials (Table 2).

Meta-analysis was performed to evaluate the effect of tirzepatide on reduction in body weight compared with single GLP-1 receptor agonists. Five randomised controlled trials were included in the quantitative synthesis. Analyses were conducted using a random-effects model and stratified by tirzepatide dose (5 mg, 10 mg, and 15 mg) to avoid duplication of comparator arms.

Five studies [17–21]contributed data to the 15 mg subgroup, including 826 participants in the tirzepatide group and 823 participants in the comparator group. Tirzepatide 15 mg was associated with a significantly greater reduction in body weight compared with single GLP-1 receptor agonists, with a pooled mean difference of − 7.43 kg (95% CI − 9.37 to − 5.49). The overall effect was statistically significant (Z = 7.50, p < 0.00001), with substantial heterogeneity observed (I^2 = 89%).

Three studies [17–19] contributed data to the 10 mg subgroup, comprising 659 participants receiving tirzepatide and 668 participants receiving comparator therapy. Tirzepatide 10 mg resulted in a significantly greater reduction in body weight compared with single GLP-1 receptor agonists, with a pooled mean difference of − 6.02 kg (95% CI − 8.78 to − 3.26). The overall effect was statistically significant (Z = 4.27, p < 0.0001), with substantial heterogeneity present (I^2 = 93%).

Three studies [17–19] contributed data to the 5 mg subgroup, including 667 participants in the tirzepatide group and 668 participants in the comparator group. Tirzepatide 5 mg demonstrated a significantly greater reduction in body weight compared with single GLP-1 receptor agonists, with a pooled mean difference of − 3.03 kg (95% CI − 5.68 to − 0.39). The overall effect was statistically significant (Z = 2.25, p = 0.02), with substantial heterogeneity observed (I^2 = 92%).

A statistically significant difference was observed between dose subgroups (χ^2 = 6.89, df = 2, p = 0.03; I^2 = 71%). The forest plot summarising pooled estimates for body-weight reduction across dose subgroups is presented in Fig. 3B.

Figure 3B

Forest plot showing pooled mean differences in body-weight reduction comparing tirzepatide with single glucagon-like peptide-1 receptor agonists, stratified by tirzepatide dose.

Figure 3A

Forest plot showing pooled mean differences in HbA1c reduction comparing tirzepatide with single glucagon-like peptide-1 receptor agonists, stratified by tirzepatide dose.

4. Discussion

In the present analysis, tirzepatide demonstrated a consistently greater reduction in HbA1c compared with single GLP-1 receptor agonists across all analysed doses. The pooled mean differences were − 0.95% for 5 mg, − 0.89% for 10 mg, and − 0.94% for 15 mg, with overlapping confidence intervals across dose groups. Subgroup analysis showed no evidence of between-dose heterogeneity, indicating that the comparative glycaemic benefit of tirzepatide over GLP-1 receptor agonists was similar across the therapeutic dose range in pooled head-to-head analyses.

However, results from individual randomised controlled trials showed that absolute HbA1c reductions generally increased numerically with higher tirzepatide doses within the same study. The apparent difference between individual-study dose patterns and pooled meta-analytic estimates arises from the design of the present analysis. Specifically, this meta-analysis compared tirzepatide with active GLP-1 receptor agonists administered at different doses across trials and was not designed to evaluate within-tirzepatide dose–response relationships. As a result, pooled estimates reflect relative efficacy versus active comparators rather than intrinsic dose-dependent effects of tirzepatide.

Incretin-mediated insulin secretion and glucagon suppression are glucose-dependent processes and exhibit saturable receptor signalling, such that once substantial glycaemic improvement is achieved, further increases in agonist exposure yield diminishing incremental reductions in HbA1c [22]. As a result, greater absolute HbA1c reductions observed with higher tirzepatide doses in individual trials may not translate into proportionally larger between-group differences in pooled comparative analyses, particularly when assessed against active GLP-1 receptor agonists.

In both individual trials and pooled analyses, tirzepatide produced progressively greater reductions in body weight with increasing dose when compared with single GLP-1 receptor agonists. The pooled mean differences were − 3.03 kg for 5 mg, − 6.02 kg for 10 mg, and − 7.43 kg for 15 mg. Unlike the HbA1c outcome, a clear dose–response relationship was observed for weight loss, supported by significant between-dose heterogeneity on subgroup analysis ($\chi^2 = 6.89$, $P = 0.03$). This pattern indicates that body-weight outcomes are more sensitive to incremental tirzepatide exposure than glycaemic outcomes. This may reflect the combined activation of GLP-1 and GIP receptors, which has been associated with greater

suppression of energy intake and improvements in β-cell function and insulin sensitivity, thereby supporting larger and more sustained reductions in body weight than GLP-1 receptor agonism alone [23].

Heterogeneity in HbA1c outcomes was substantial across dose-specific analyses, with I^2 values of 69% for 5 mg and 95% for both 10 mg and 15 mg. Although pooled estimates showed similar magnitudes of HbA1c reduction across doses (approximately − 0.9 to − 1.0%), the apparent consistency of pooled effects therefore reflects the comparative nature of the analysis rather than absence of dose-related effects. The observed heterogeneity is likely attributable to between-study differences in baseline HbA1c, trial duration, and variation in GLP-1 receptor agonist comparator type and dosing, rather than true variability in the glycaemic effect of tirzepatide.

Body-weight outcomes demonstrated high heterogeneity across all doses, with I^2 values of 92% at 5 mg, 93% at 10 mg, and 89% at 15 mg. This variability is likely attributable to differences in baseline body weight, lifestyle interventions, treatment duration, and variation in control-arm GLP-1 receptor agonist type and dose, all of which directly influence weight-loss magnitude. Importantly, despite high heterogeneity, the direction of effect consistently favoured tirzepatide across all doses, indicating that heterogeneity reflects differences in effect size rather than inconsistency in treatment benefit. However, because all included studies were direct head-to-head randomised controlled trials conducted within a single trial protocol, background diabetes management, including lifestyle counselling such as diet and physical-activity advice, was applied similarly to participants across treatment arms within each study. Therefore, these co-interventions are unlikely to have systematically favoured either treatment group.

Several previous systematic reviews have evaluated tirzepatide in adults, but they differ in analytical focus and study design. One review focused on weight-loss outcomes only [11], whereas others assessed both HbA1c and body weight but used broader frameworks [13, 14], including mixed comparator groups, indirect comparisons, small numbers of included trials, and short follow-up durations. A study by Alhussain Khawaji et al. [11] focused on weight loss outcomes and compared tirzepatide against single GLP-1 receptor agonists. Tirzepatide produced dose-dependent weight reductions of − 3.03 kg, − 6.02 kg, and − 8.31 kg at 5 mg, 10 mg, and 15 mg, respectively. This dose-dependent pattern closely aligns with the present study, which demonstrated corresponding weight reductions of − 3.03 kg, − 6.02 kg, and − 7.43 kg across the same dose range. Zhou et al. [13] conducted a broad meta-analysis including trials with multiple comparator arms GLP-1 receptor agonists, insulin, and placebo. Their synthesis also incorporated adjusted indirect treatment comparisons, which rely on cross-trial statistical linkage rather than direct randomisation, and included studies with short follow-up durations of eight weeks. Within this design, HbA1c reduction appeared to increase with higher tirzepatide doses, whereas the incremental weight-loss benefit was greater at lower doses and diminished at higher doses. In contrast, the present study restricted inclusion to direct head-to-head GLP-1 receptor agonist trials with a minimum follow-up of 24 weeks and demonstrated HbA1c reductions that were consistent with those reported by Zhou et al., alongside a clear dose-dependent increase in body-weight loss. Study by Bhagvathula et al. [14] included four trials, two comparing tirzepatide with GLP-1 receptor agonists and two with placebo. In this review, both body-weight reduction

and HbA1c reduction increased with higher tirzepatide doses, which is consistent with the findings of the present study. However, dose-specific interpretation was limited by the small evidence base, with only a single study contributing data to the 5 mg dose arm. In addition, weight-loss estimates at 10 mg and 15 mg were very similar (− 8.64 kg vs − 8.67 kg), indicating limited separation between higher doses in that review. In contrast, the present study demonstrated clearer differentiation between the 10 mg and 15 mg doses, with pooled weight reductions of − 6.02 kg and − 7.43 kg, respectively, supporting a more distinct dose-related pattern.

These findings have important clinical implications for the use of tirzepatide in adults with type 2 diabetes. Across head-to-head trials, tirzepatide consistently achieved greater reductions in both HbA1c and body weight compared with single GLP-1 receptor agonists, with increasing absolute reductions observed at higher doses. Notably, body-weight outcomes demonstrated greater sensitivity to dose escalation than glycaemic outcomes, indicating that incremental increases in tirzepatide exposure translate more clearly into additional weight loss than into further HbA1c reduction. This distinction supports an individualised approach to dosing, whereby patients with marked obesity or weight-related cardiometabolic risk may derive greater benefit from higher doses, while patients with less excess weight but poor glycaemic control may achieve clinically meaningful HbA1c reductions at lower doses. Overall, these results support flexible titration of tirzepatide based on patient phenotype and treatment priorities and reinforce the clinical value of dual incretin receptor agonism in the management of type 2 diabetes.

To our knowledge, this is the first systematic review and meta-analysis to synthesise evidence exclusively from direct head-to-head randomised controlled trials comparing tirzepatide with single GLP-1 receptor agonists. Inclusion was limited to randomised controlled trials, ensuring a high level of internal validity, and treatment effects were directionally consistent across all included studies. Focusing on direct comparisons avoids dilution of treatment effects that can arise when placebo- and insulin-controlled trials are combined. Dose-specific analyses enabled clear evaluation of differential glycaemic and weight responses across the therapeutic range, while applying a minimum treatment duration of 24 weeks ensured that outcomes reflected sustained rather than short-term effects. Together, these design features enhance the clinical relevance and interpretability of the findings for treatment selection within incretin-based therapies. Having outlined these strengths, several limitations should be acknowledged. Only five trials met the inclusion criteria, which limited statistical power and precluded formal assessment of publication bias. Substantial heterogeneity was observed, particularly for weight outcomes, likely reflecting clinical and methodological differences across studies, including variation in baseline patient characteristics, trial duration, and the type and dosing of GLP-1 receptor agonist comparators. Although dose-stratified analyses were performed, formal dose–response meta-regression was not conducted; therefore, the analysis was not designed to quantify intrinsic dose–response relationships for tirzepatide independent of comparator effects. In addition, one included trial employed a fixed dose-escalation protocol, which may have influenced observed treatment effects [21]. Adverse event outcomes were not quantitatively synthesised, limiting conclusions regarding comparative tolerability. Finally, all included trials were industry funded by Eli Lilly and Company, the manufacturer of

tirzepatide. However, according to trial registry information, principal investigators were not employed by the sponsor.

Future research should prioritise larger head-to-head randomised controlled trials directly comparing tirzepatide with individual GLP-1 receptor agonists using standardised and equivalent comparator dosing. Such designs would allow clearer separation of true tirzepatide dose effects from variability introduced by differing comparator dose intensities. Longer follow-up durations are also required to assess the durability of both glycaemic control and weight reduction beyond the timeframes currently available. In addition, future meta-analyses incorporating formal dose–response modelling, such as meta-regression, would help quantify the relationship between tirzepatide dose and metabolic outcomes when comparator effects and background therapies are adequately controlled. Further studies should also explore sources of heterogeneity identified in the present analysis, including baseline metabolic status, trial design, and dose-escalation strategies, to better inform personalised treatment selection and optimise clinical decision-making.

5. Conclusion

This systematic review and meta-analysis synthesised evidence exclusively from direct head-to-head randomised controlled trials comparing tirzepatide with single GLP-1 receptor agonists in adults with type 2 diabetes mellitus, with inclusion restricted to studies of at least 24 weeks' duration to capture sustained treatment effects. Across all included trials, tirzepatide consistently produced significantly greater reductions in both glycated haemoglobin and body weight than GLP-1 receptor agonists, demonstrating superior overall metabolic efficacy. Increasing tirzepatide dose was associated with greater absolute improvements, and weight-related outcomes showed a more pronounced sensitivity to dose escalation. Taken together, these findings support the metabolic advantages of dual GIP and GLP-1 receptor agonism over selective GLP-1 receptor activation and highlight tirzepatide as an effective therapeutic option for adults with type 2 diabetes.

Declarations

Funding

This research received **no external funding**.

Conflicts of Interest

The authors declare **no conflicts of interest**.

Ethical Approval

Ethical approval was not required for this study because it was a systematic review and meta-analysis based exclusively on data from previously published studies and publicly available clinical trial registries.

Informed Consent

Informed consent was not required for this study as no new data were collected and no individual participant-level data were accessed or analysed.

Data Availability Statement

All data analysed in this study were derived from published literature and publicly accessible clinical trial registries.

Author Contributions

Osama Omar Khan: Conceptualization, Writing – original draft, Investigation, Methodology, Validation, Visualization, Writing – review & editing, Software, Formal analysis, Data curation, Project administration, Resources.

Syed Baqir Ali Shah: Writing – original draft, Methodology, Validation, Writing – review & editing, Investigation, Data curation, Visualization.

Human ethics and consent to participate
Not applicable.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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Tables

Tables are available in the Supplementary Files section.

Figures

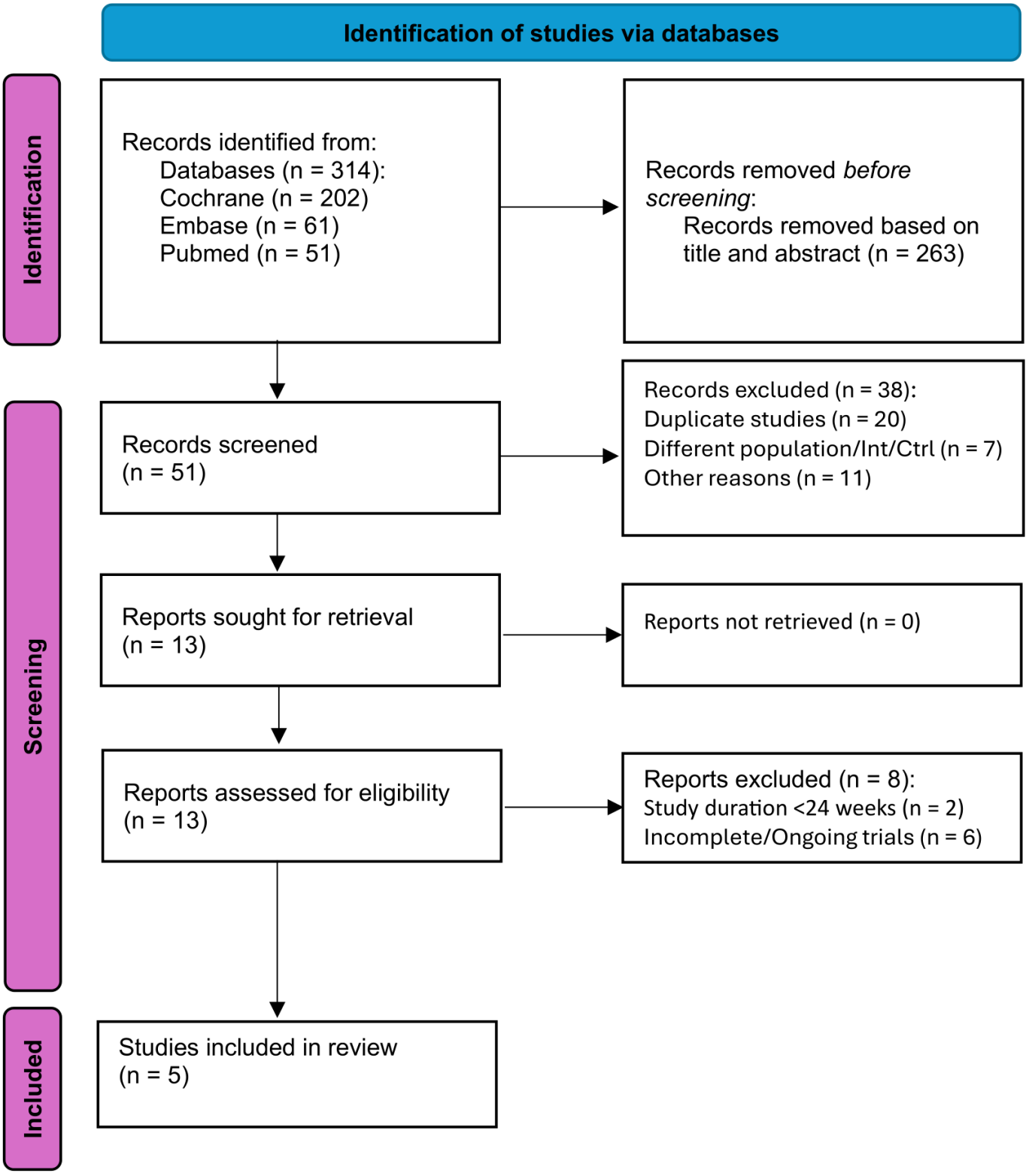


Figure 1

PRISMA flow diagram illustrating the study selection process for the systematic review and meta-analysis. Database searches were conducted up to **31 October 2025**, showing the number of records identified, screened, excluded, and included at each stage.

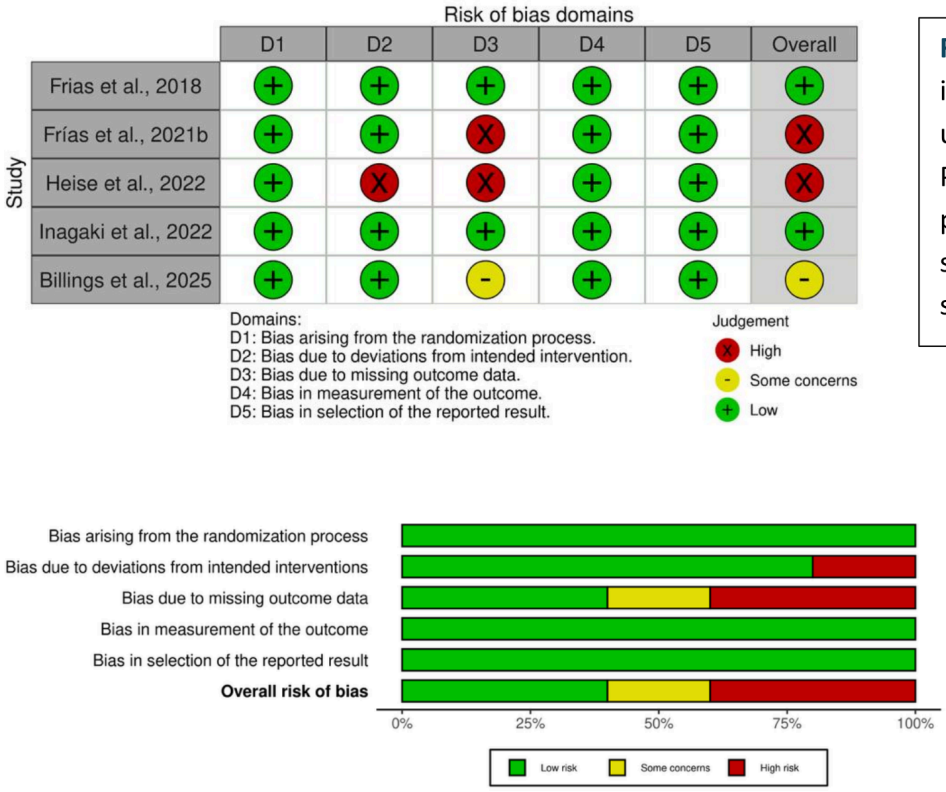


Figure 2. Risk of bias assessment of included randomised controlled trials using the Cochrane Risk of Bias 2.0 tool. Panel A shows the risk-of-bias traffic light plot, and Panel B shows the risk-of-bias summary across all domains for each study.

Figure 2

See image above for figure legend

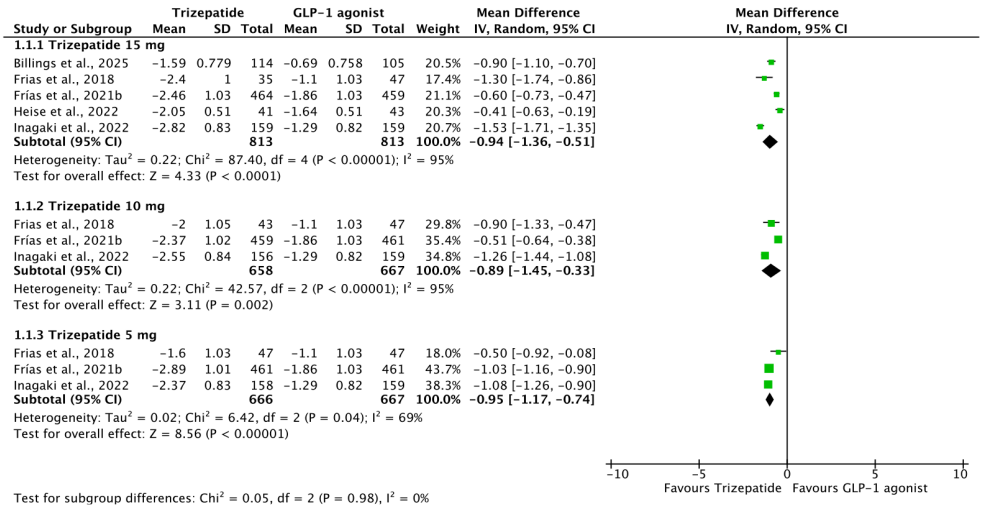


Figure 3A: Forest plot showing pooled mean differences in HbA1c reduction comparing tirzepatide with single glucagon-like peptide-1 receptor agonists, stratified by tirzepatide dose.

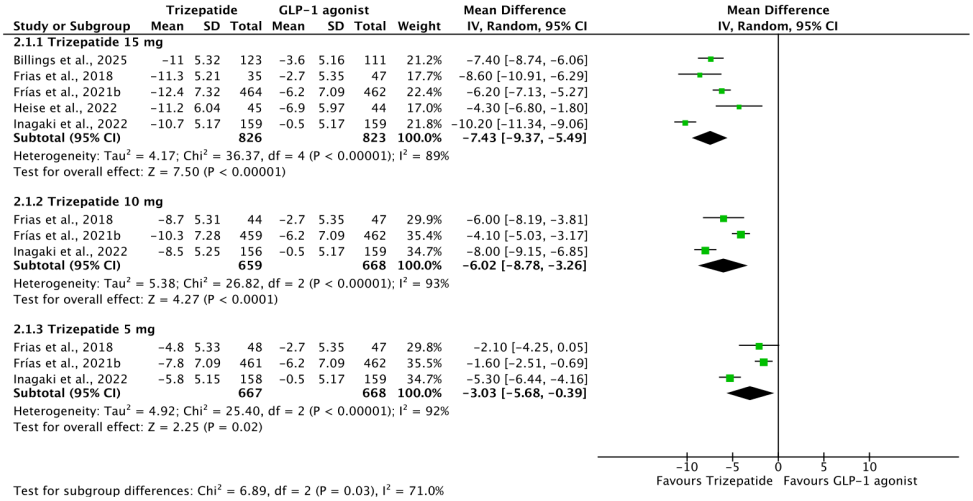


Figure 3B: Forest plot showing pooled mean differences in body-weight reduction comparing tirzepatide with single glucagon-like peptide-1 receptor agonists, stratified by tirzepatide dose.

Figure 3

See image above for figure legend

Supplementary Files

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- Table12.docx